MANAGEMENT OF TYPE 2 DIABETES

If HbA1c > 53mmol/mol (7%)

FIRST LINE ADD METFORMIN or Sulfonylurea if intolerant of metformin

SECOND LINE OPTIONS

ADD SULFONYLUREA
+ COST EFFECTIVE
- Consider alternatives options where hypo-glycaemia or weight gain are a concern (see table A).

ADD GLITAZONE
+ Useful treatment for patients with fatty liver and NASH
- WEIGHT GAIN & COST
Fluid retention and increased risk of cardiac failure. Increased risk of fracture in post-menopausal women (see table A) Possible increased risk of bladder cancer Withdraw treatment after 6 months if HbA1c has decreased by < 0.5% (5.5 mmol/mol).

ADD GLIPTIN
Use only if major reservations re metformin, sulfonylureas or pioglitazone
+ Unlikely to cause hypoglycaemia Weight neutral
- COST
Withdraw treatment after 6 months if HbA1c has decreased by < 0.5% (5.5 mmol/mol).

THIRD LINE OPTIONS

If HbA1c > 59 mmol/mol (7.5%)

ORAL ADMINISTRATION

ADD GLITAZONE
When subcutaneous agent is not acceptable (see table A).
Weigh up positive and negative factors as for 2nd line treatment.

ADD GLIPTIN
When subcutaneous agent is not acceptable (see table A).
Weigh up positive and negative factors as for 2nd line treatment.

ADD GLP-1 analogue
If BMI >30kg/m² and weight loss desirable (see table A) When hypoglycaemia is a concern (see table A) Maximum dose of liraglutide =1.2mg Treatment target is HbA1c reduction of 11mmol/mol (1%) AND weight loss of 3% of initial body weight

SUBCUTANEOUS ADMINISTRATION

ADD INSULIN
If HbA1c is > 9.0% (75mmol/mol) oral agents will not fully correct.
Use insulin when there is clear progression of the disorder.

ADD GLP-1 analogue
If BMI >30kg/m² and weight loss desirable (see table A) When hypoglycaemia is a concern (see table A) Maximum dose of liraglutide =1.2mg Treatment target is HbA1c reduction of 11mmol/mol (1%) AND weight loss of 3% of initial body weight

If HbA1c > 59 mmol/mol (7.5%) change to insulin +/- metformin

If HbA1c > 59 mmol/mol (7.5%) Intensify insulin treatment

If HbA1c > 59 mmol/mol (7.5%) consider insulin therapy

Means advantageous
- Means disadvantageous
Table A

<table>
<thead>
<tr>
<th>Special Considerations</th>
<th>Examples</th>
<th>Drug(s) indicated</th>
<th>Drug(s) to be used with caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemia</td>
<td>Vocation (drivers)¹, living alone (especially elderly)</td>
<td>Metformin, Pioglitazone</td>
<td>Sulfonylureas, Insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gliptins, GLP-1 analogues</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>BMI&gt;30 in Caucasians, BMI&gt;28 in South Asians, Obstructive sleep apnoea</td>
<td>Metformin, Gliptins, GLP-1 analogues</td>
<td>Sulfonylureas, Glitazones, Insulin</td>
</tr>
<tr>
<td>Subcutaneous administration unacceptable</td>
<td>Needle phobia, frail or elderly leading to loss of independence</td>
<td>Metformin, Sulfonylureas, Gliptins, Pioglitazone</td>
<td>Insulins, GLP-1 analogues</td>
</tr>
<tr>
<td>Risk of bone fractures</td>
<td>Postmenopausal females, known osteoporosis, alcoholism, hypothyroidism</td>
<td>Metformin, Sulfonylureas, Gliptins, Pioglitazone</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>Risk of bladder cancer</td>
<td>Known bladder cancer, undiagnosed macroscopic haematuria</td>
<td>Metformin, Sulfonylureas, Gliptins, GLP-1 analogue</td>
<td>Pioglitazone</td>
</tr>
</tbody>
</table>

OPTIONS FOR FIRST LINE THERAPY

**Monotherapy**

Following the diagnosis and introduction of lifestyle changes, if HbA1C > 53mmol/mol (7.0%) consider starting an oral hypoglycaemic agent. Lifestyle changes should be encouraged and continued throughout all the stages of management of type 2 diabetes. Patients should receive initial advice from a state registered dietician. Those not responding to dietary advice and who meet the criteria should be considered for referral to the Glasgow Weight Management Program (see appendix 10).

**Metformin is first line therapy in combination with lifestyle changes**

Commence 500mg in the morning for first week and titrate upwards 500mg twice daily for a further week then 500mg three times daily. The dose may be further increased to a usual maximum of 2g daily, though specialists have used up to 3g daily. See BNF for contra-indications to metformin.

Metformin is contra-indicated in renal impairment, serum creatinine > 130 micro mol/l, (eGFR <30mls/min) and severe liver disease. There is an increased risk of lactic acidosis in renal impairment although the incidence of lactic acidosis attributable to metformin is very rare. NICE recommends reviewing the dose of metformin if eGFR less than 45ml/minute and to avoid if eGFR is less than 30ml/minute..

If HbA1c remains at or below 53mmol/mol (7.0%) continue to review the patient 6 monthly. Metformin has clinically relevant cardiovascular outcomes.

**Sulfonylurea (SU) 1st line therapy if metformin not tolerated or contra-indicated.**

Commence Gliclazide at 40 to 80 mg with breakfast. The dose can be further increased to 160 mg with breakfast or in divided doses. The maximum dose is 320mg daily in divided doses, the last dose usually with the early evening meal.

Gliclazide is the formulary preferred list SU. Glipizide and Glibenclamide are in the total formulary. However Glibenclamide a long acting SU is not used in the elderly because of a higher incidence of hypoglycaemia.

OPTIONS FOR SECOND LINE THERAPY

Dual Therapy

If adequate glycaemic control is not maintained on one agent (HbA1c > 53mmol/mol (7.0%) then dual therapy is necessary. The addition of a sulfonylurea or a glitazone to metformin therapy should be considered. The preferred agent will depend upon the individual patient and the relative indications and contra-indications for sulfonylureas, glitazones and gliptins. Gliptins should not be considered as second line therapy unless there are major reservations with the prescription of metformin, sulfonylureas or pioglitazone.

Note that the addition of a second oral agent (sulfonylurea, pioglitazone or gliptin) is likely to improve HbA1c by no more than 9.0 – 16mmol/mol (0.8 – 1.5%).

Refer to the BNF for a full list of cautions and contraindications.

Sulfonylureas  augment insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present. The major side-effects are hypoglycaemia and weight gain. The incidence of hypoglycaemia reported in a population study was 1%. Sulfonylureas are contra-indicated in severe hepatic and renal impairment. Sulfonylureas have no proven benefit on cardiovascular outcomes. Sulfonylureas are a cost effective treatment option.

Glitazones  Pioglitazone is the only drug of this class now available. It is associated with fluid retention and has precipitated heart failure and pulmonary oedema in patients at risk. It is contra-indicated in heart failure (NYHA class 1 to IV) or left ventricular dysfunction and should be avoided in hepatic impairment. Subgroup analysis of the PROACTIVE study has shown that pioglitazone significantly reduces the risk of recurrent stroke and recurrent MI in high risk patients. Pioglitazone is associated with an increased risk of upper limb fractures. The European Medicines Agency has recently issued recommendations for pioglitazone in order to reduce a possible, small increased risk of bladder cancer. Prescribers should not use pioglitazone in patients with current or a history of bladder cancer or in patients with uninvestigated macroscopic haematuria. Risk factors for bladder cancer should be assessed before initiating this therapy. The use of this medication in the elderly who have increased risk of bladder cancer, should be carefully considered. Pioglitazone should be started at a dose of 15mg daily. Its maximum effect will take 4 – 6 weeks and the dose should not be increased until after this interval. The dose can be increased to 30mg and if necessary to 45mg once daily. Check LFTs before use and periodically thereafter. At present all suspected adverse reactions should be reported by the yellow card scheme to the Commission on Human Medicines.

Gliptins  GLIPTINS SHOULD NOT BE CONSIDERED AS SECOND LINE THERAPY UNLESS THERE ARE MAJOR RESERVATIONS WITH THE PRESCRIPTION OF METFORMIN, SULFONYLUREAS OR PIOGLITAZONE.
Gliptins are orally active inhibitors of dipeptidylpeptidase-4 resulting in increased levels of GLP1. There are no long term data on cardiovascular outcomes for this group of medications. Their advantages are that they are likely to be weight neutral and unlikely to cause hypoglycaemia. Restricted to specialist initiation for patients on metformin only when the addition of sulfonylureas or pioglitazone is not appropriate. **Only continue treatment after 6 months if HbA1c has decreased by 5.5 mmol/mol (0.5%).** If this reduction is not achieved then the gliptin should be stopped.

Sitagliptin is a once daily preparation while vildagliptin is a twice daily preparation. Vildagliptin requires 3 monthly monitoring of liver function during the first year and periodically thereafter. Linagliptin is a once daily preparation and can be used in moderate to severe renal impairment without change to normal dose. Saxagliptin is also once daily and has a licence for use at half normal dosage in moderate to severe renal impairment. Saxagliptin is currently the cheapest of this class. Refer to BNF for all cautions in renal and hepatic impairment.

At present all suspected adverse reactions should be reported by the yellow card scheme to the Commission on Human Medicines.

**OPTIONS FOR THIRD LINE THERAPY**

**Triple Therapy**

If HbA1c is > 59 mmol/mol (7.5%) on two oral hypoglycaemic agents then the addition of a third agent can be considered. If patients are on metformin plus sulfonylurea then consider adding glitazone. Similarly a sulfonylurea can be added to the combination of metformin plus glitazone. Alternatively, a gliptin could be introduced as a third agent. Oral agents and GLP-1 analogues are unlikely to reduce HbA1c levels by more than 9.0 – 16mmol/mol (0.8 – 1.5%) although the higher the initial level of HbA1c the greater is the subsequent drop with treatment. If HbA1c is therefore above 75mmol./mol (9%) on two agents do not consider triple therapy and move directly to insulin treatment.

**GLP-1 Analogues**

Exenatide and Liraglutide are glucagon like peptide 1 (GLP1) analogues which increases insulin secretion, delay gastric emptying and suppresses glucagon secretion. Treatment with a GLP1 is associated with the prevention of weight gain and possible promotion of weight loss. They are available as subcutaneous injections. There is no outcome data for this class of drugs.

GLP-1 analogues should only be considered in patients with a BMI >30Kg/m².

GLP-1 analogues should be used initially over a 6 month trial period. The treatment should be continued after this period only if targets are achieved. These would be a reduction in HbA1c of at least 11mmol/mol (1%) and weight loss of 3% or more of initial body weight. Treatment must be reviewed every 6 months and if efficacy is waning treatment should be changed to insulin therapy.

**Restricted to specialist initiation as an alternative to insulin in patients who have failed treatment on (metformin and sulfonylureas) dual therapy and in whom insulin would be the next treatment option.**

At present all suspected adverse reactions should be reported by the yellow card scheme to the Commission on Human Medicines.
The Introduction of Insulin

If there is suboptimal control with two (or three) oral hypoglycaemic agents or if dual therapy is contraindicated then insulin should be introduced with one oral hypoglycaemic agent, preferably metformin.

Acarbose

Acarbose is less effective than other oral hypoglycaemic agents but may be prescribed by specialists in addition to other agents for patients intolerant of metformin.

Nateglinide and Repaglinide

These drugs are not on the GGC Formulary. Any exceptional use of these medicines should be subject to GGC non-Formulary processes.